Asthma management and device selection in adults

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TRENDS IN ASTHMA PREVALENCE, MORBIDITY AND MORTALITY
Components of the asthma guidelines (Expert Panel Report-3 EPR-3 2007)

https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma

- Measures of Asthma Assessment and Monitoring
- Environmental factors
- Treatment
- Education for a partnership
Diagnosis of asthma

The diagnosis of asthma should be based on:
- A history of characteristic symptom patterns
- Evidence of variable airflow limitation, from bronchodilator reversibility testing or other tests

Document evidence for the diagnosis in the patient’s notes, preferably before starting controller treatment
- It is often more difficult to confirm the diagnosis after treatment has been started

Asthma is usually characterized by airway inflammation and airway hyperresponsiveness, but these are not necessary or sufficient to make the diagnosis of asthma.

Measures of lung function in asthma

PEAK FLOW
- Used only for monitoring
- Can provide falsely high or falsely low readings
- More erroneous measures in children compared to adults
- SYMPTOM BASED ACTION PLAN IS PREFERABLE
- Efforts cannot be quality assured

SPIROMETRY
- Used for diagnosis and monitoring
  - 12% improvement in the FEV₁ pre-post SABA
  - If – BD response, is asthma ruled out?
  - FEV₁/FVC is better for determining severity
  - FEV₁ is better for predicting an exacerbation
- Efforts can be quality assured
Severity

Control
<table>
<thead>
<tr>
<th>Condition</th>
<th>Well-Controlled</th>
<th>Partially Well-Controlled</th>
<th>Partially Uncontrolled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exertional</td>
<td>On exertion only</td>
<td>On exertion only</td>
<td>Frequent</td>
<td>Continuous</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Slight</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very Severe</td>
</tr>
<tr>
<td>Use of Medications</td>
<td>On occasion</td>
<td>Frequent</td>
<td>Daily</td>
<td>Constant</td>
</tr>
<tr>
<td>Treatment</td>
<td>Standard</td>
<td>Increased</td>
<td>Enhanced</td>
<td>Maximal</td>
</tr>
<tr>
<td>Prevention</td>
<td>Basic</td>
<td>Enhanced</td>
<td>Advanced</td>
<td>Maximal</td>
</tr>
</tbody>
</table>

**Asthma Control Test™ (ACT)**

1. Are you able to play or participate in strenuous physical activity without having an asthma attack? (Max 4)
2. Are you able to do most of your usual activities without being limited by your asthma? (Max 4)
3. Are you able to sleep through the night without using an inhaler? (Max 4)
4. Are you able to do everything you want to do without having an asthma attack? (Max 4)
5. Are you able to go about your daily activities without worrying about having an asthma attack? (Max 4)

**Score Interpretation**
- **Asthma Control**: 13-16
- **Asthma Poor**: 0-8
- **Asthma Moderate**: 9-12

**Note**: The score range is not provided in the current state of the document. It is recommended to consult the manufacturer's instructions for normal scores ranges.
Goals of asthma treatment

- Few asthma symptoms
- No sleep disturbance
- No exercise limitation
- Maintain normal lung function
- Prevent flare-ups (exacerbations)
- Prevent asthma deaths
- Avoid medication side-effects

The patient's goals may be different from these
Symptoms and risk may be discordant – need to assess both

Terminology

Uncontrolled asthma
- Frequent symptoms and/or flare-ups (exacerbations)
  - Many of these patients may potentially have mild asthma, i.e. their asthma could be well-controlled with low dose ICS, if taken regularly

Difficult-to-treat asthma
- Not difficult patients
- Asthma uncontrolled despite prescribing high dose preventer treatment
- Contributory factors may include incorrect diagnosis, incorrect inhaler technique, poor adherence, comorbidities

Severe asthma
- "Severe asthma" has had many different meanings (Spici CI, 2008; Nishit AIRES, 2008)
  - Now defined as asthma that is uncontrolled despite maximal optimised therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased (Chung, 2014)
  - i.e. relatively refractory to corticosteroids (very completely refractory)
- A retrospective definition, dependent on how thoroughly contributory factors are excluded
**Phenotype**: The observable characteristics of a disease, such as morphology, development, biochemical or physiological properties, or behaviour.
- Patients with an identified phenotype of obstructive lung disease may share a cluster of clinical, functional and/or inflammatory features, without any implication of a common underlying mechanism.
- Examples: allergic asthma, aspirin-exacerbated respiratory disease, severe eosinophilic asthma.

**Endotype**: A subtype of disease, defined functionally and pathologically by a distinct molecular mechanism or by distinct treatment responses.
- Among patients with obstructive lung disease, there are likely to be several specific endotypes associated with divergent underlying molecular causes, and with distinct treatment responses. These endotypes may or may not align with clinical or inflammatory phenotypes identified from studies limited to asthma or COPD.
- Examples: emphysema due to alpha1-antitrypsin deficiency.

**Biomarker**: A defined characteristic measured as an indicator of normal biologic processes, pathogenic processes or response to an intervention.
- Potential examples: FeNO, blood eosinophils – but these may not meet quality criteria for biomarkers.

The future of treatment won’t be focused on severity.
Pharmacologic Therapy as per GINA 2019

Common treatments for the medical management of Asthma

- **Quick-relief “rescue”**
  - Short-acting bronchodilators (prn)
  - SABAs (beta 2 agonists - preferred)
  - "Burst" of systemic corticosteroids

- **Long-term control**
  - Inhaled corticosteroids (ICS)
  - Long-acting muscarinic antagonist (LAMA)
  - Combination therapy (inhaled corticosteroids and long-acting beta 2 agonist (ICS/LABA)
  - Leukotriene modifiers
  - Long-acting agents

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**SABAs**
Common treatments for the medical management of Asthma

**Quick relief “rescue”**
- Inhaled corticosteroids (ICS)
- Short-acting beta 2 agonists (SABAs) preferably
- "Burst" of systemic corticosteroids

**Long-term control**
- Combination therapy (inhaled corticosteroids and long-acting beta 2 agonists (ICS/LABA)
- Leukotriene modifiers
- Biologic agents

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Mechanism of Action: short-acting beta 2 agonists

- Cholinergic nerve
- Antimuscarinics
- Smooth muscle
- Relaxation
**SABAs**

- MDIs
- DPIs
- Nebulizers
- Breath-actuated DPI
  - Digihaler

<table>
<thead>
<tr>
<th>SOLUTIONS (ALVESCO)</th>
<th>SUSPENSIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvesco</td>
<td>All other MDIs are suspensions</td>
</tr>
<tr>
<td>No need to shake</td>
<td>Have to be shaken between puffs</td>
</tr>
<tr>
<td>&lt; 2 microns in size</td>
<td>&gt; 3 microns in size – reach bronchial/conducting tubes</td>
</tr>
<tr>
<td>reach smaller airway</td>
<td></td>
</tr>
</tbody>
</table>

Breath-actuated DPI that provides a timestamp, inspiratory flow feedback and companion app connected via Bluetooth.
Background to changes in 2019 - the risks of ‘mild’ asthma

Patients with apparently mild asthma are at risk of serious adverse events
- 30–37% of adults with acute asthma
- 10% of patients with near-fatal asthma
- 15–20% of adults dying of asthma

Exacerbation triggers are variable (viruses, pollens, pollution, poor adherence)

Inhaled SABA has been first-line treatment for asthma for 50 years
- This dates from an era when asthma was thought to be a disease of bronchoconstriction
- Patients satisfaction with, and reliance on, SABA treatment is reinforced by its rapid relief of symptoms, its prominence in ED and hospital management of exacerbations, and low cost
- Patients commonly believe that “My reliever gives me control over my asthma”, so they often don’t see the need for additional treatment

Background to changes in 2019 - the risks of SABA-only treatment

Regular or frequent use of SABA is associated with adverse effects
- β2-receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response (Drugs, 2000)
- Increased allergic response, and increased eosinophilic airway inflammation (Drugs, 2000)

Higher use of SABA is associated with adverse clinical outcomes
- Dispensing of ≥3 canisters per year (average 1.7 puffs/day) is associated with higher risk of ED visit and hospital presentation
- Higher use of SABA is associated with higher risk of death (Suissa, AJRCCM 2012)
Since 2007, GINA has been actively seeking interventions for mild asthma
- to reduce the risk of asthma-related exacerbations and death
- to provide consistent messaging about the goals of asthma treatment, including prevention of exacerbations, across the spectrum of asthma severity
- to avoid establishing patient reliance on SABA early in the course of the disease

GINA emphasized poor adherence as a modifiable risk factor for exacerbations
- When the reliever is SABA, poor adherence with maintenance controller exposes the patient to risks of SABA-only treatment

GINA members repeatedly sought funding for RCTs of as-needed ICS-formoterol for risk reduction in mild asthma
- Eventually culminated in 2014 with the initiation of the SYGMA studies, published in 2018 (O’Byrne NEJM 2018; Bodmer NEJM 2018)

In the meantime, GINA challenged conventional criteria for initiation of ICS
- During preparation for 2014 GINA revision, we identified no evidence for the recommendation to withhold ICS until symptoms were more than twice weekly
- This was investigated in data from the START study (Pauwels, Lancet 2003). A post hoc analysis found that ICS halved the risk of serious exacerbations even in patients with symptoms 0-1 days a week at entry (Reddel, Lancet 2017)

GINA found no evidence to support a Step 1 SABA-only recommendation
- The lack of evidence for SABA-only treatment contrasted with the strong evidence for safety, efficacy and effectiveness of treatments recommended in Steps 2-5
- In 2014, as an interim safety measure, GINA restricted SABA-only treatment to patients with symptoms less than twice a month and no risk factors for exacerbations

2018: Review of evidence for mild asthma, including SYGMA studies
- A careful review of GINA conflict of interest processes was undertaken first

For safety, GINA no longer recommends SABA-only treatment for Step 1
- This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk

GINA now recommends that all adults and adolescents with asthma should receive symptom-driven or regular low dose ICS-containing controller treatment, to reduce the risk of serious exacerbations
- This is a population-level risk reduction strategy, e.g. statins, anti-hypertensives

GINA 2019 – landmark changes in asthma management
Step 1 – ‘preferred’ controller option

Step 1 is for patients with symptoms less than twice a month, and with no exacerbation risk factors

As needed low dose ICS-formoterol (off-label)

Evidence
- Indirect evidence from PIRENA I of large reduction in severe exacerbations vs SABA-only treatment in patients eligible for Step 2 therapy (O’Byrne, NEJM 2018)

Values and preferences
- High importance given to reducing exacerbations
- High importance given to avoiding conflicting messages about goals of asthma treatment between Step 1 and Step 2
- High importance given to poor adherence with regular ICS in patients with infrequent symptoms, which would expose them to risks of SABA-only treatment
**MDIs**
**DPIs**
**Nebulizers**
**Breath-actuated MDI (Redihaler)**

*Single agent ICS*

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**New esters**

- Arnuity Ellipta - different fluticasone esters (furoate vs. propionate)
- FF confers higher affinity for lung tissue compared with FP
- Translates to enhanced lung residency and once-daily efficacy in asthma
- Some evidence that the characteristics of FF may result in superior symptom reduction compared with FP

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“Most patients with asthma do not need more than low-dose ICS”

“For most asthma patients, controller treatment can be started with either low-dose ICS-formoterol or with regular daily low dose ICS.”
Effects of ICS on inflammation

Low-dose ICS and the prevention of death from asthma in Canada

Rate Ratio for Death from Asthma

Number of Canisters of ICS per Year
Step 2 – there are two ‘preferred’ controller options

**Regular low dose ICS with as-needed SABA**

**Evidence**
- A large body of evidence from RCTs and observational studies that low dose ICS substantially reduces risks of severe exacerbations, hospitalizations and death (e.g. Suissa, NEJM 2000; Suissa, Thorax 2002; Pauwels, Lancet 2003; O’Byrne, Am J Resp 2003)
- Serious exacerbations halved even in patients with symptoms 0–1 days per week (Reddel, Lancet 2017)
- Improved symptom control and reduced exercise-induced bronchoconstriction

**Values and preferences**
- High importance was given to preventing asthma deaths and severe exacerbations
- However, we were aware that poor adherence is common in mild asthma in the community, and that this would expose patients to the risks of SABA-only treatment

**As-needed low dose ICS (formoterol; all evidence with budesonide-formoterol)**

**Evidence**
- Direct evidence from two large studies of non-inferiority for severe exacerbations vs daily low dose ICS + as-needed SABA (O’Byrne, NEJM 2018; Bateman, NEJM 2018)
- Direct evidence from one large study of 64% reduction in severe exacerbations vs SABA-only treatment (O’Byrne, NEJM 2018)
- Symptoms reduced; one study showed reduced exercise-induced bronchoconstriction

**Values and preferences**
- High importance was given to preventing severe exacerbations, avoiding need for daily ICS in patients with mild or infrequent symptoms, and safety of as-needed ICS-formoterol in maintenance and reliever therapy, with no new safety signals
- Lower importance given to small non-cumulative differences in symptom control (ACQ-5 difference 0.15 vs MCID 0.5) and lung function compared with daily ICS
- Makes use of normal patient behavior (seeking symptom relief) to deliver controller
Mechanism of Action: long-acting beta 2 agonists (SABAs) + ICS + LABA combos

MDIs

DPIs

ICS + LABA combos

NEW ULABAS
Vilanterol in Breo

NEW COMBOS
Wixela (generic Advair) in new DPI device (inhub)
Mechanism of Action:
long-acting muscarinic antagonist

- MDIs SAMA for asthma
- DPIs LAMA
- Nebulizer (SAMA for asthma)
- SMIls Respimat soft mist inhaler
- LAMAs single agent and combos
New triple therapy  UICS + ULABA + ULAMA

Trelegy

**STEP 1**
- As-needed low dose ICS - formoterol

**STEP 2**
- Low dose ICS - LABA

**STEP 3**
- Medium dose ICS - LABA

**STEP 4**
- High dose ICS, add-on tiotropium, or add-on LTRA

**STEP 5**
- Add low dose OCS, but consider side effects

**Other controller options**

**Other reliever option**

**PREFERRED RELIEVER**

**PREFERRED CONTROLLER**

**Confirmation of diagnosis**
- if necessary

**Symptom control & modifiable risk factors (including lung function)**

**Comorbidities**

**Inhaler technique & adherence**

**Patient goals**

**Treatment of modifiable risk factors & comorbidities**

**Non-pharmacological strategies**

**Education & skills training**

**Asthma medications**

1 © Global Initiative for Asthma, www.ginasthma.org
Anti-IgE biologic - omalizumab (Xolair)

Monoclonal antibody for those
- 6 and older
- With severe persistent asthma
- Which cannot be controlled on conventional therapies

1-3 injections every 2-4 weeks based on IgE levels and weight
Serum IgE rises
Black box warning
- Carry epipen
Interleukin (IL)-5

IL-5 is a cytokine produced by a number of cells
Essential for the maturation of eosinophils in the bone marrow and their release into the blood
IL-5 acts only on eosinophils and basophils causing maturation, growth, activation and survival
Only eosinophils and basophils possess IL-5 receptors

Anti-IL-5 biologics

Monoclonal antibody for those
- Severe persistent asthma w/an eosinophilic phenotype (eos > 150 cells/μL) who cannot be controlled on conventional therapies
- Serum eosinophils decrease

Anti-II5s

- Monoclonal antibody for those
  - Severe persistent asthma w/an eosinophilic phenotype (eos > 150 cells/μL) who cannot be controlled on conventional therapies
  - Serum eosinophils decrease
Anti-IL4s

Anti-IL-4/13 biologic - dupilumab (Dupixent)

Binds IL-4 and IL-13 receptor, two cytokines that contribute to the inflammation in asthma

Indicated for those 12 and older with mod- to severe asthma

Bronchial thermoplasty

Indicated for adults with severe asthma - radio frequency energy applied to airway wall to decrease smooth muscle

Treat airways > 3 mm during three separate procedures (RLL, LLL, R/LUL) at 2-3 week intervals
Bronchial Thermoplasty

Other changes in GINA 2019

Updated strategies for 'yellow zone' of action plans, with new evidence

- 4x increase in ICS dose decreased severe exacerbations in pragmatic study in adults (McKeever, NEJMed 2018)
- 5x increase in ICS dose did not decrease severe exacerbations in children with good symptom control and high adherence (Jackson, NEJMed 2018)